The Bitter Substance, Produced in Black-rotten Sweet Potato. III. On the Constitution of Ipomoeamarone. Part 2.

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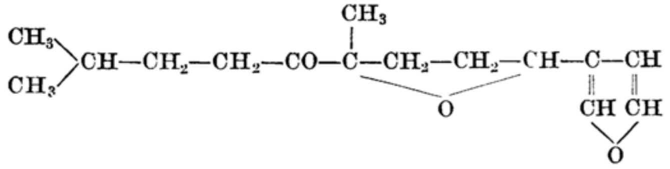
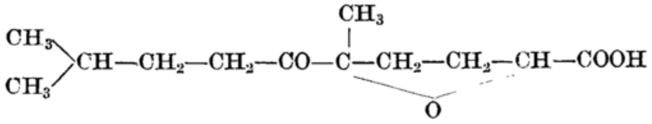
It was shown in our previous report⑴ that ipomoeamarone was an open-chain sesquiterpenic compound containing a ketonic group, two oxide rings and two ethylenic linkages. It gave a keto-acid (named ceratonic acid) and oxalic acid by oxidation with potassium permanganate at room temperature, and gave acetone, acetic acid, oxalic acid and a liquid



I.



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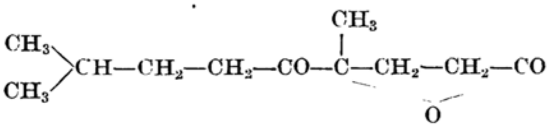

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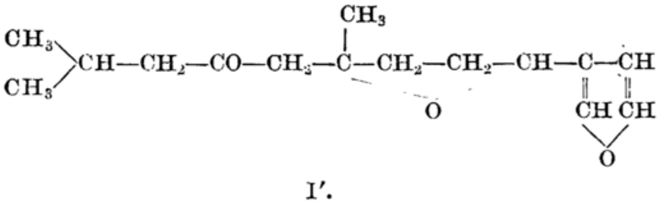
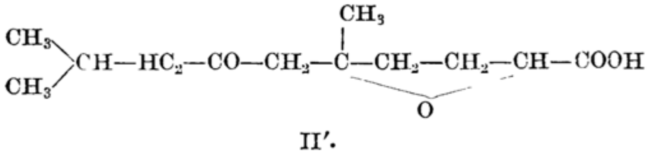
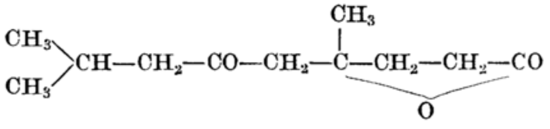


I′.



II′.



III′.

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(1) T. Ohno, This Bulletin **25**, 222-225 (1952).

acid by the same oxidation procedure at 100°.

At the general meeting of the Agricultural Chemical Society of Japan, held at Tokyo on April 5, 1952, we proposed tentatively formula I for ipomoeamarone, II for ceratonic acid, and III for the keto-lactone, the latter two of which were the degradation products of the former by oxidation with potassium permanganate.

T. Kubota and his collaborators of the Osaka City College of Polytechnics also announced the results of their own research on ipomoeamarone at the general meeting of the Chemical Society of Japan, held at Tokyo on April 3, 1952, and put forward the formulae of ipomoeamarone (I′), ipomeanic acid (II′) and ipomic lactone (III′), the latter two of which were ozonolysis products of the former.

Some part of their results, including the structures of ipomeanic acid and ipomic lactone, has already been published,(2)(3) and their report read at the general meeting of the Chemical Society of Japan was published recently(4).

Though, between Kubota et al. and us, there is an essential disagreement in the interpretation of the structure of ipomoeamarone, we wish to postpone detailed discussion of this and to publish our results read at the general meeting of the Agricultural Chemical Society of Japan as it stands.

As regards the nomenclature of the substances, we think it preferable to use "ceratonic acid", because this name apparently was in print prior to "ipomeanic acid", but we agree with Kubota et al. in adopting the name "ipomic lactone" for the keto-lactone (III or III′).

By oxidation of ipomoeamarone with potassium permanganate at room temperature, a non-volatile liquid acid showing ketonic color reaction was obtained. This was converted into *p*-phenylphenacyl ester (m. p. 79°) and by its analysis a molecular formula, $C_{12}H_{20}O_4$, can be given to the acid. However, neither crystalline semicarbazone nor 2, 4-dinitrophenylhydrazone of the acid was obtained. It is now obvious from the results of following experiments that this acid retains the original ketonic and oxidic groups, both present in ipomoeamarone. This acid was named ceratonic acid in our previous paper, and may be identical with the ipomeanic acid of Kubota et al.

Ipomoeamarone semicarbazone was now oxidized in dilute acetone with potassium permanganate at room temperature, and a crystalline semicarbazone and a mixture of non-volatile liquid acids were obtained. The former was identified with the semicarbazone of ceratonic acid (ipomeanic acid), $C_{13}H_{23}O_4N_3$, m. p. 172°, $[\alpha]_D^{24}=-86.7°$ (in alcohol and pyridine, 4:1). The latter, admixed with some of this crystalline semicarbazone, was then hydrolysed with dilute sulfuric acid in methanol, and fractionated into two parts. The lower boiling fraction (b. p. 99—103°/0.3mm.) coincided with the formula $C_{11}H_{18}O_3$ and was considered to be a keto-lactone, because of its difficult neutralizability at room temperature. It gave positive color reaction for a ketone, but its 2, 4-dinitrophenylhydrazone was a liquid and semicarbazone crystallized only partially This lactone was considered to be the ipomic lactone of Kubota et al. The higher boiling fraction, (b. p. 123—135°/0.3 mm.), ceratonic acid, accorded with $C_{12}H_{20}O_4$; *p*-phenylphenacyl ester melted at 79°, and is identical with the ester of the acid, obtained by direct oxidation of ipomoeamarone; the semicarbazone melted at 172° and is identical with the above mentioned semicarbazone. The non-volatile acid was thus proved to be a mixture of ipomic lactone and ceratonic acid.

Ipomoeamarone was treated with phenylmagnesium bromide, and the resulting compound was dehydrated with acetic anhydride and zinc chloride, followed by oxidation with potassium permanganate. Formic, isovaleric, and oxalic acids were obtained besides a non-volatile acid and a lactone.

From the properties of these degradation products obtained by various oxidation methods, it is concluded that: (1) Ceratonic acid is an open-chain acid containing the original ketonic group and one of the original oxide rings, losing three carbon atoms, two ethylenic linkages and an oxide oxygen, and ipomoeamarone possesses therefore, beyond all doubt, a furan-nucleus involving a carbon atom which might have been converted to a carboxylic group of ceratonic acid and three other carbon atoms which might have been lost by oxidation. That is, ipomoeamarone is a furan derivative substituted at α or β position with a side chain of C_{11} which contains a ketonic group and an oxide ring. (2) Ipomic lactone, which is a carbon shorter than ceratonic acid, retains also an original ketonic group, the oxide ring of ceratonic acid being transformed into a lactone ring. The carbon atom of α-position of ceratonic acid may therefore be a

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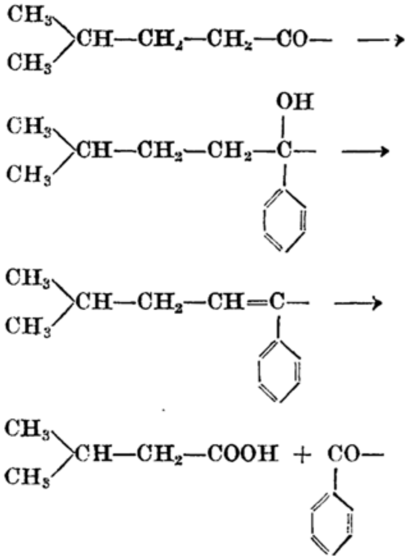
(2) T. Kubota and T. Matsuura, *Proc. Japan Acad.* **28**, 44-47 (1952). They proposed the name "Ipomeamarone" instead of "Ipomoeamarone" for the sake of simplifying the spelling.

(3) T. Kubota and T. Matsuura, ibid. **28**, 83-84 (1952).

(4) T. Kubota and T. Matsuura, ibid. **28**, 198-199 (1952).

secondary one, with which oxide oxygen connects, and the oxide ring forms a hydrofuran-nucleus, because the properties of the lactone is considered to be a γ-lactone. (3) The formation of isovaleric acid by the oxidation of the reaction product of Grignard's reagent may establish the constitution of ipomoeamarone to be an isoamyl ketone, and the reaction involved would have taken place in the following manner;



Ipomoeamarone gave dark green color in the pine-shaving test, and an adduct with maleic anhydride, although in a liquid form. In addition, the facts that absorption of hydrogen proceeds only slowly by catalytic reduction, the unsuccessfulness of obtaining dihydro-compound, and the stability of double bonds against sodium ethanolate reduction, are only understood by assuming that two ethylenic linkages of ipomoeamarone form a furan-nucleus.

In consequence, if ipomoeamarone is presumed to be a sesquiterpene derivative and to have a skeleton of an oridinary openchain three-isoprene-structure, such as farnesol or nerolidol, the conclusion may be drawn from the results that ipomoeamarone has a tentative formula (I), ceratonic acid (II), and ipomic lactone (III), respectively.

The only difference between the constitutional formulae of ipomoeamarone of Kubota and of us is the position of ketonic group, and it will be discussed in a future communication.

Experimental

(1) **Ipomoeamarone semicarbazone.**—The yield of semicarbazone by the pyridine-method (see our last communication) from the crude bitter oil was as follows; 60—70 g. of crude semicarbazone from 100 g. fraction 1 (b. p. 140—145°/7 mm.). This product gave 21—25 g. of pure crystals by recrystallization; 80—90 g. of crude semicarbazone from 100 g. fraction 2 (b. p. 145—150°/7 mm.), giving 28—31 g. of pure crystals by recrystallization.

(2) **Hydrolysis of ipomoeamarone semicarbazone.** (a) **By oxalic acid.**—A mixture of the semicarbazone (20 g.) and oxalic acid (30 g.) in water (1 l.) was boiled vigorously for one hour. The product was isolated by means of ether, and ether was washed with aqueous alkali and evaporated. Pure ipomoeamarone (13.6 g.) was obtained by vacuum distillation (yield; 83.4%).

(b) **By potassium bisulfate.**—A mixture of the semicarbazone (5 g.) in benzene (80 cc.) and potassium bisulfate (25 g.) in water (50 cc.) was shaken at room temperature for 175 hours. The benzene layer was separated, washed with saturated sodium bicarbonate solution followed by drying with anhydrous sodium sulfate. After the complete removal of benzene, petroleum ether was added and undecomposed semicarbazone (1 g.) precipitated was filtered off. Free ipomoeamarone was obtained as colorless oil after vacuum distillation of the filtrate; b. p. 112—3°/0.6 mm., $[\alpha]_D^{20}=+11.07°$ (c, 2.8 in benzene). (Found: C, 72.24; H, 8.62. Calc. for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80%

(3) **Oxidation of ipomoeamarone.**—Free ipomoeamarone (2.0 g.), which was regenerated from the semicarbazone, was suspended in water (100 cc.), and powdered potassium permanganate was added to the mixture in small portions under shaking and occasional cooling. After 6 g. of potassium permanganate (corresponding to 7.1 atoms of oxygen) were added, no further decolorisation occurred. Manganese dioxide was then filtered off and washed with hot water. The filtrate and washings were combined, concentrated, decolorized with active charcoal, extracted with ether to remove neutral substances, and acidified with concentrated hydrochloric acid. The separated oil was extrated twice with chloroform, and dried with anhydrous sodium sulfate. A brown viscous acid (1.6 g.) was obtained after the removal of chloroform. The liquid acid showed positive color reaction for ketone with sodium nitroprusside, although it gave no crystalline semicarbazone. Its *p*-bromophenacyl ester was liquid, but *p*-phenylphenacyl ester was obtained as leaflet crystals mixed with oily substance, m. p. 79° from alcohol. Analysis showed that the ester corresponds to the formula $C_{26}H_{30}O_5$, showing that the acid is $C_{12}H_{20}O_4$. (Found: C, 73.43; H, 6.98. Calc. for $C_{26}H_{30}O_5$: C, 73.94; H, 7.11%)

It is obvious that the acid, as shown in the next experiment, preserves the original ketonic group and one of the oxide rings, and we proposed the name ceratonic acid to this acid in our previous paper. It may be the same compound as the ipomeanic acid of Kubota et al.

The aqueous layer, separated from chloroform solution, was neutralized with aqueous ammonia, and a solution of calcium chloride was added to it. Calcium oxalate was precipitated; 0.16 g. (namely 0.16 equivalent).

(4) Oxidation of ipomoeamarone semicarbazone.—To a solution of ipomoeamarone semicarbazone (20 g.) in acetone (200 cc.), treated beforehand with potassium permanganate, water (200 cc.) was added, followed by the addition of powdered potassium permanganate in small portions under shaking and occasional cooling. Forty-seven grams (equivalent to 6.85 atoms of oxygen) were consumed. After manganese dioxide was decomposed by passing sulfur dioxide gas through the reaction mixture, it was concentrated to half its volume under diminished pressure, and inorganic substances were filtered off and washed with ether. The filtrate was extracted repeatedly with ether, the combined ether extract was washed with 10% sodium hydroxide solution repeatedly, and 3.6 g. of a neutral oil, which crystallized immediately, was obtained after evaporation; colorless powder, m. p. 119° (from ether and petroleum ether). Mixed melting point determination and analytical value showed that it was the unreacted semicarbazone. (Found: C, 62.78; H, 7.98; N, 13.48. Calc. for $C_{16}H_{25}O_3N_3$: C, 62.54; H, 8.14; N, 13.68%)

Aqueous layer mixed with sodium hydroxide solution was acidified with dilute sulfuric acid, fractionating into a part soluble in ether and crystals soluble in ether with difficulty. The latter was ceratonic acid semicarbazone; colorless powder from ether, m. p. 172° (decomp.), $[\alpha]_D^{24}=-86.7°$ (*c*, 6.0 in ethanol and pyridine, 4:1). (Found: C, 54.81, 54.51; H, 8.57, 7.94; N, 14.97, 14.73. Calc. for $C_{13}H_{23}O_4N_3$: C, 54.74; H, 8.07; N, 14.74%) The former was a viscous liquid (11 g.) admixed with some crystals of the semicarbazone. The oil was refluxed with 25% sulfuric acid (50 cc.) in methanol (100 cc.) for 3 hours, the methanol was removed, and the separated oil was extracted with ether and the ether extract distilled in a vacuum. A viscous oil (6.6 g.) was obtained; b. p. up to138°/0.15 mm., $[\alpha]_D^{20}=+18.0°$ (*c*, 2.0 in ether). *p*-Phenylphenacyl ester melted at 79°, which was identical with the ester above mentioned, was contaminated by an oily substance; no crystallien semicarbazone was obtained. By analysis of the acid it was shown to be a mixture of two substances, $C_{12}H_{20}O_4$ and $C_{11}H_{18}O_3$. (Found: C, 64.54, 64.24; H, 9.59, 9.19. Calc. for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Calc. for $C_{11}H_{18}O_3$: C, 66.67; H, 9.07%.)

The mixture of the acid (5.0 g.) was fractionated as follows: (A) b. p. 99—103°/0.3 mm., 2.5 g., (B) b. p. 103—123°/0.3 mm., 0.5 g., (C) b. p. 123—135°/0.3 mm., 1.5 g. The first fraction, a pale yellow mobile oil, was considered to be a lactone, because it was neutralized with N/10 potassium hydroxide solution only when warmed. *p*-Phenylphenacyl ester was not obtained. The first and second fraction in ether were treated with sodium bicarbonate solution to remove acidic substances if any, and the lactone was obtained by shaking it repeatedly with 10% sodium hydroxide solution, followed by acidifying, extracting with ether, and distilling in vacuo, b. p. 134—140°/4 mm., 1.0 g. (Found: C, 67.01; H, 9.00. Calc. for $C_{11}H_{18}O_3$: C, 66.76; H, 9.09%)

The lactone gave a color reaction with sodium nitroprusside, but the semicarbazone was crystallized only partially. The 2,4-dinitrophenylhydrazone remained oily; yellow crystals, which were formed in an alcoholic solution by cooling with a mixture of dry ice and ether, melted at room temperature. This ketolactone may be the same compouud as the ipomic lactone of Kubota et al.

The third fraction, a viscous yellow oil, proved to be ceratonic acid. The acid was converted into *p*-phenylphenacyl ester, m. p. 79° and also into semicarbazone, m. p. 168° (decomp.); these proved to be identical with the derivatives which were mentioned above, respectively. Analysis of the oil corresponds to $C_{12}H_{20}O_4$. (Found: C, 63.20; H, 8.69. Calc. for $C_{12}H_{20}O_4$: C, 63.16; H, 8.78%)

(5) Reaction of phenylmagnesium bromide upon ipomoeamarone and oxidation of the product by potassium permanganate.—To an ice-cooled solution of ipomoeamarone (5.6 g., regenerated from the semicarbazone) in ether was added a solution of phenylmagnesium bromide in ether (2.7 N, 15 cc.) dropwise and the mixture was refluxed for 30 minutes. The reaction product was poured into a mixture of ice and dilute sulfuric acid. The ethereal layer was separated, washed with saturated bicarbonate solution, and dried. To the viscous product obtained by removal of the ether, 4 g. of acetic anhydride and a small portion of zinc chloride were added. After refluxing for 30 minutes, the mixture was poured into water. Ether was added, washed with 10% potassium hydroxide solution and dried. The removal of the ether left 6 g. of a viscous dark-brown oil.

The oil obtained was oxidized with potassium permanganate in dilute pyridine (100 cc. pyridine and 300 cc. water). Thirteen grams of potassium permanganate were required (corresponding to 6.8 atoms of oxygen). Manganese dioxide was now removed by filtration and washed with hot water. From the filtrate and washings pyridine was distilled off with steam. The residual solution, after concentration to half its volume, was treated with ether to remove non-volatile neutral substances (0.1 g.), and the aqueous layer was distilled with steam after acidification. The distillate was neutralized and treated with potassium permanganate solution for decomposition of formic acid. The filtrate from manganese dioxide was concentrated to dryness, acidified, and extracted with ether. The volatile acid (250 mg.) was converted to *p*-bromophenacyl ester, m. p. 64°. This was proved to be the ester of isovaleric acid by mixed melting point determination and analysis. (Found: C, 52.00; H, 5.60. Calc. for $C_{13}H_{15}O_3Br$: C, 52.17; H, 5.02. Calc. for $C_{12}H_{13}O_3Br$: C, 50.53; H, 4.56%) The mixed melting point with the ester of isobutyric acid showed a depression of about 10°.

From the residual solution of steam-distillation, there were obtained a non-volatile acid (0.9 g.), a lactone (0.1 g.) and oxalic acid.

Summary

By oxidation of ipomoeamarone and its semicarbazone with potassium permanganate, ceratonic acid (ipomeanic acid) (II), $C_{12}H_{20}O_4$, and ipomic lactone (III), $C_{11}H_{18}O_3$, were obtained. The ketonic group of ipomoeamarone was proved to be an isoamyl ketone by the oxidation of the reaction product of Grignard's reagent. These experiments led us to conclude that ipomoeamarone is represented by the provisional constitution (I).

We wish to express our sincere gratitude to Prof. S. Takei and Dr. M. Ohno of the University of Kyoto for their guidance and to Dr. M. Matsui of our Laboratory for his helpful advice given to us during our research.

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